REMARKS

Status of the Claims

Claims 1-4 were pending.

Claim 1 was withdrawn from consideration.

Claims 2-4 stand rejected.

Claim 4 is amended.

Claims 2-3 are canceled.

Claims 5-13 are new claims.

Reconsideration is respectfully requested.

Response to Section 112 Rejection

Claims 2-3 stand rejected under Section 112 for expressing exemplary language and preferences. Applicant gratefully thanks the Examiner for pointing out these issues. Claims 2-3 have been canceled and while the subject matter thereof is included in new claims 5 and 10, respectively, the objectionable language was not included in the newly-presented claims.

Claim Amendments and New Claims

Claim 4 is amended to place that claim in independent form. Otherwise, the scope of claim 4 is unchanged. Claims 5 and 10 correspond substantially in scope with previous claims 2 and 3 respectively, although applicant has amended these claims for clarity and to recite the invention with greater focus and particularity in view of the specific Examples set forth in the specification herein. Dependent claims 6 through 9 and 11 through 12 are included to define the invention in various ways, *e.g.*, with different scope. The formulae and groups recited in these dependent claims are supported by the specific Examples set forth in the specification herein.

Response to Section 103 Rejection

The Office Action rejected previous claims 2-4 as allegedly obvious on two grounds, (1) in view of Miller, WO 99/32463 (Office Action, p. 4, paragraph 9-11), and (2) on the ground that "fused succinimide substituted ureas are known generally for treating cancer."

(*Id.*, paragraph 12). Since claims 5 and 10 are similar in scope to previous claims 2 and 3, the applicant addresses those rejections below.

The obviousness inquiry under *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 693 (1966), requires that the decision-maker consider: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the field at the time the invention was made, and (4) objective evidence of secondary considerations. *Id.; see also Para-Ordnance Mfg. v. SGS Importers Intern.*, 73 F.3d 1085, 1088, 37 USPQ2d 1237 (Fed. Cir. 1995). Against this backdrop, obviousness is determined. In considering a conclusion of obviousness, the Federal Circuit has established three essential findings for the USPTO to meet, as a minimum, to establish a *prima facie* case of obviousness, *i.e.*, that: (1) the prior art contains a suggestion or motivation for modifying or combining the references; (2) the proposed modifications have a reasonable expectation of success in the prior art; and (3) the references teach or suggest *all* claim limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The initial burden of satisfying these requirements rests squarely with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142.

Notably, in *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999), the Federal Circuit emphasized that it will demand a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art cases." *Id.* at 1617. This is necessary, the court explained, to guard against the "subtle but powerful attraction of a hindsight-based obviousness analysis." *Id.* Thus, under *In re Dembiczak*, for the Examiner to make a *prima facie* obviousness determination, the Examiner must make "particular findings" based on "actual evidence," and the "showing must be clear and particular." *Id.* at 1617. Conclusory statements that are unsupported by actual evidence and particular findings are "entirely inadequate to support the rejection." *Id.* (*quoting In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977)).

The two obviousness rejections in the Office Action are not supported by actual evidence or particularized findings and are entirely inadequate to establish a *prima facie* case. None of the elements for a *prima facie* case is met.

First, the Office Action cites to Miller to argue that the instant methods are obvious. However, Miller is a patent publication pertaining to p38 kinase inhibitors wherein the core group of preferred compounds is an N,N'-diphenyl-substituted urea compound (Miller at 10). While Miller identifies a succinimide group as a possible substituent that could be attached to a phenylalkyl, phenoxy, or other phenyl-based group that is linked to one of the phenyl substituents of the central urea (p. 10), Miller's genus of compounds is significantly different from the genus of compounds recited in the claimed methods herein. Notably, the Office Action does not argue that the instantly-claimed methods involve use of compounds which are the same as, or even homologs or analogs of, the compounds of Miller, but only that Miller shows a succinimide group as a possible outermost substituent on p38-inhibiting diphenyl urea compounds.

In this vein, the Examiner's attention is respectfully directed to *In re Wagner*, 371 F.2d 877, 152 USPQ 552 (C.C.P.A. 1967). There, the court reversed a PTO conclusion of obviousness where the difference between the claimed compound and prior art compounds was the presence of two methyl substituents on a core ringed structure. *Id.*, 152 USPQ at 555. The claims recited benzimidazole derivatives substituted with at least one lower alkyl group at two specific positions. The prior art taught benzimidazole derivatives having no substituents or bearing dimethyl substituents at two *other* positions of the ring. On appeal, the CCPA pointed out that there were eleven possible locations for placement of the methyl substituents. *Id.*, 152 USPQ at 559. It specifically rejected the PTO's finding that "the modification of a compound by the addition of one or more methyl groups is well known and thus obvious," stating that such general statements cannot support legal conclusions of obviousness. *Id.* at 883-84, 152 USPQ at 559. Additionally, the Board and PTO erred, the court found, by failing to take into account biological or pharmaceutical properties of the compounds. *Id.* at 881, 152 USPQ at 557. *See also In re Ruskin*, 274 F.2d 955, 125 USPQ 13, 16 (CCPA 1960) (reversing PTO's obviousness rejection of sulfonate ester erythromycin based on disclosure of erythromycin ester analogs as there was no suggestion in the prior art for the sulfonic acid substitution); *Ex Parte Brouard*, 201 USPQ

538 (Bd. Pat. App. 1976) (reversing Examiner's obviousness rejection because substituting a hydrogen atom with a hydroxy group is not *prima facie* obvious).

As indicated by *In re Wagner*, it is well known in the field of pharmaceutical compounds, to which the instant invention pertains, that biological activity can be unpredictably connected to the location of substituents on a ring. Given that modification of a particular core structure to add two methyl groups was not sufficient to support an obviousness rejection in *Wagner*, Miller's disclosure of a succinimide group in a large genus as an outermost substituent on a diphenylurea compound cannot support an obviousness rejection in this case. The Examiner is required to consider the biological and pharmaceutical properties of the compounds. The instant case claims methods of modulating the nuclear hormome receptor and methods of treating cancer. There is no suggestion or motivation in the prior art that the succinimide group selected from all the other groups of possible outer substituents for the diphenyl-urea compound of Miller would be advantageous in developing a pharmaceutical product for the modulation of a nuclear hormone receptor and treatment of cancer.

Second, the Office Action argues that "A person of ordinary skill in the art would have been motivated to employ a fused succinimide substituted urea for treating prostate cancer because fused succinimide substituted ureas are known generally for treating cancer." (Office Action, paragraph 12). This is a conclusory statement unaccompanied by actual evidence or particularized findings. The Office Action 1) has not identified the scope and content of the pertinent prior art -- including an identification of the basis for the conclusion that "fused succinimide substituted ureas are known generally for treating cancer"; 2) has not ascertained the differences between the pertinent prior art and the instantly-claimed methods --- including an analysis of how the prior art compounds and methods differ in structure and biological activity with the instantly-claimed methods; and 3) has not identified a suggestion or motivation to modify any alleged prior art references involving fused succinimide ureas and treatment of cancer to arrive at applicant's claimed methods of modulating the nuclear hormone receptor. It is the PTO's burden to establish a *prima facie* case in the first instance.

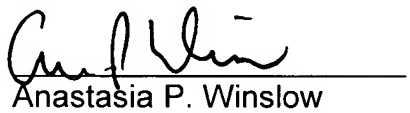
FEES

With the new claims herein, this case contains three independent claims and less than twenty claims. Thus, it is believed no fee is due. However, in the event it is determined a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb.

SUMMARY

It is believed that all rejections of the claims have been fully addressed and that the instant claims are in condition for allowance. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

Respectfully submitted,



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